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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
AKHAVAN, RAMIN	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 10/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/026,331	HITOSHI ET AL.	
	Examiner	Art Unit	
	Ramin (Ray) Akhavan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8-41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: Sequence alignment.

DETAILED ACTION

Receipt is acknowledged of a response, filed July 15, 2005, canceling claims 1-7, 42-52, and amending claims 8, 11, 14, 16, 31, 32 and 41. Claims 8-41 are currently pending and under consideration in this action.

All objections/rejections not repeated herein are hereby withdrawn. Where applicable, a response to Applicant's arguments will be set forth immediately following the body of any objections/rejections repeated herein. As new grounds of rejection are set forth that were not necessitated by amendment, this action is non-final.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. **Claims 8-41 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.**

This is a new ground of rejection. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. More particularly independent claims 8 and 41 are literally directed to *any* amino acid sequence of *any* size encoded by *any* nucleic acid that hybridizes under stringent conditions to the nucleic acid encoding SEQ ID NO: 2. The limitation "hybridizes" is not exclusively defined in the specification nor delimited in the claim.

Furthermore, even if the specific conditions were delimited the claims would still encompass *any* sequence hybridizes over any localized portion of SEQ ID NO: 2. In either case, the claims are directed to tremendously large number of structures that must correlate to the functionality of encoding an MRE11 protein. In other words, the claims encompass a very large genus of nucleic acid structures that encode an MRE11 protein thus necessarily encode a protein with MRE11 functionality.

To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.*, (CAFC) 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); *In re Gosteli* , 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("The description must clearly allow persons of ordinary skill in the art to recognize that (the inventor) invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious" and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Supra, Lockwood,* 107 F.3d at 1572, 41 USPQ2d at 1966. Furthermore, the Guidelines for Written Description state, "The claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art" (Federal Register/ Vol. 66, No. 4/Friday, January 5, 2001/Notices, column 1, page 1105). The Guidelines further state, "[t]he claim as a whole, including all limitations found in the preamble, the transitional phrase, and the body of the claim, must be sufficiently supported to satisfy the written description requirement" (at page

1105, center column, third full paragraph). In sum, an applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations. *Supra, Lockwood*, 107 F.3d at 1572, 41 USPQ2d 1961 (at 1966).

In the context of the instant claims, the critical or essential elements are at minimum the minimal or conserved nucleic acid sequences (i.e., structures) that correlate to any MRE11 functionality and hybridize to any portion of the nucleic acid encoding the amino acids of SEQ ID NO: 2 (i.e., DNA of SEQ ID NO: 1). The only disclosed embodiment is that of SEQ ID NO: 1. No additional structures are identified nor is additional evidence presented in the specification that clarifies or identifies what particular sequences or regions within SEQ ID NO: 1 are conserved or necessary so as to correlated to MRE11 functionality. In fact, the number of potential species encompassed by the claimed genus is further amplified insofar as the claims are directed to any functionality that is ascribed to MRE11 whether indirectly or directly. (e.g., Specification, ¶ 0056; note: all references to the specification correspond to the published version of this application, i.e., USPG. PUB. NO. 2003/0027167). Therefore, the required level of description in the specification or in the relevant art is increased even to an even higher level. Given that the instant disclosure provides a single example for such a tremendously large genus of structures, there is a notable gap in the specification regarding description of sufficient or representative number of embodiments.

There is evidence in the art demonstrating that MRE11 correlates to various functions in a cell and even that there may be organism-specific functions, wherein the functionalities include DNA-binding activities, strand-annealing activities, DNA nuclease activity and non-homologous recombination. (e.g., Petrini, Am. J. Hum. Genet. 1999; 64:1264-69; discussing MRE11 function

in DNA-damage response and DNA repair; Furuse et al. EMBO *J.* 1998; 17:6412-25; discussing distinct roles of two separable *in vitro* activities of yeast MRE11 in mitotic and meiotic recombination; de Jager et al. Nuc. Acids Res. 2001; 29:1317-25; discussing DNA-binding and strand annealing activities of human MRE11; Moreau et al. Mol. Cell. Biol. 1999; 19:556-566; discussing MRE11 nuclease activity). However, there does not appear to be any evidence in the art to demonstrate the identity of particular conserved sequences that correspond to a given function. Furthermore, there does not appear to be any evidence to suggest that there is a representative structure common to all MRE11 proteins across any species of organism, whereby said structure correlates to any one of the preceding multiple functions ascribed to MRE11. Moreover, because many of MRE11 functions are not ascribed to MRE11 alone, but rather, MRE11 functioning in a complex of proteins (e.g., complex with RAD50 and XRS2 proteins), then the description must necessarily take into account that portions of MRE11 that are necessary for protein-protein binding would also have to be clarified (e.g., through mutational or deletion analysis). (e.g., Paull et al. Genes Dev. 1999; 13:1276-88; teaching that the Mre11/Rad50/Nbs1 complex displays several distinct enzymatic activity that are not observed without Nbs1). In other words, in the context of the instant claimed methods, the necessary and critical elements would regarding independent claims 8 and 41 include nucleic acids that not only encode a functional motif but also a motif that is necessary and sufficient to bind partner proteins so as to form the necessary complex in the first place.

In sum, given the very limited disclosure of a single species, given the enormous breadth of the structures necessary to practice the, and encompassed by, the rejected claims, and the skilled artisan would not have been able to envision a sufficient number of specific embodiments

to described the broadly claimed genus of nucleic acids hybridizing to any nucleic acid encoding any polypeptide sequence within SEQ ID NO: 2.

Moreover, an applicant claiming a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from other species. Therefore, the skilled artisan would reasonably have concluded that applicants were not in possession of the claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

2. Claims 8-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

This is a new ground of rejection. Independent 8 is directed to a method for "identifying a compound that modulates cellular proliferation or chemosensitivity". However, the body of the claim does not interrelate with the preamble, because the final action step is directed to determining a functional effect of the compound upon MRE11. (*See*, claim 41). Thus, it is unclear what is being claimed (e.g., method of assaying a compound for modulation of cellular proliferation or determining an effect on MRE11). For example, pouring bleach into a culture dish would certainly modulate cellular proliferation or chemosensitivity and would also certainly have a "functional effect" on MRE11. As written, the claim is vague and indefinite.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

2. **Claims 8-12, 14-17, 19, 27, 29, 32, 35, 38, 39 rejected under 35 U.S.C. 102(a) as being anticipated by Lanson et al. (Nuc. Acids Res. 2000; 28:2882-92).**

The limitation with respect to SEQ ID NO: 2 is interpreted to mean a sequence with any level of homology (i.e., hybridizing) to any local region within a nucleic acid encoding SEQ ID NO: 2. The limitation "stringent" is not particularly limiting, since essentially stringency can be measured in a gradient (e.g., low, moderate, high, very high, extremely high stringency, etc.). The specification does not provide a specific and exclusive definition for the limitation "stringent"[1]. The limitation "contacting a compound" is interpreted as broadly as reasonable to include any compound present in any form and contacted in any way.

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[1] See, Specification, ¶ 0078: "The phrase 'stringent hybridization conditions' refers to conditions under which a probe will hybridize to its target subsequence, typically in a complex mixture of nucleic acids, but to no other sequences".

Lanson teaches a method where a compound is contacted with rat MRE11 and its effects on MRE11 are determined. Based on the sequences disclosed with overall sequence homology for MRE11, the rat MRE11 disclosed inherently comprises at least some sequences that meet the claimed limitation of hybridizing to a sequence to a nucleic acid encoding any polypeptide sequence of SEQ ID NO: 2. (e.g., p. 2886, Figure 2; depicting the rat sequence as compared to the human sequence; claims 8, 35).

More particularly, the reference teaches a method where the MRE11-NBS1-RAD50 pathway is studied and it is determined whether SV40 large T antigen (T-ag)-immortalized cells perturb said pathway as well as to determine effects on cell proliferation. (e.g., Abstract). Thus, MRE11 is contacted with T-ag in cells expressing T-ag. (e.g., col. 2883, under Cell Culture; claims 8, 38, 39).

The effects on MRE11 are measured *in vitro*, such as through SDS-PAGE and autoradiography. (e.g., p. 2883, col. 2; bottom half; claims 9-10, 12, 15). Furthermore physical effects, such as antibody binding to MRE11, are also determined. (e.g., p. 2884, col. 1; claims 9-12, 15-17). In addition, MRE11 is expressed in eukaryotic host cells. (e.g., p. 2883, col. 1; claim 14). Furthermore, the cells are cancer cells and are transformed with SV40 T-ag. (Id.) (claims 27, 29). In addition, the cells contain/express p53. (e.g., p. 2883; col. 2; claim 32). The reference also teaches that cell proliferation is measured. (e.g., p. 2889, under Discussion through to p. 2890; claim 19). In sum, the reference anticipates the rejected claims.

3. **Claims 8-12, 14-17, 19, 23-30, 34-36 and 38-40 are rejected under 35 U.S.C. 102(e) as being anticipated by Morris et al. (US 2002/0182586).**

This rejection is of record and repeated herein. A response to Applicant's arguments is set forth immediately following the body of this rejection. (Infra, Response to Arguments). The claims are interpreted consonant with the interpretations stated above.

Additional claims delimit the encoded protein (e.g., MRE11) as being recombinant, the cancer cell is HeLa cell, or a p53 null cancer cell, the screening assay further measures a substrate or ligand binding to the MRE11 protein and the candidate compound is an antisense molecule.

Morris et al. teach a method of screening drug candidates comprising providing a cell that expresses a carcinoma associate (CA) gene and also inhibiting cell proliferation. (e.g., ¶¶0007-8). The methods of screening include screening a bioactive agent capable of binding to a CA protein (CAP). (e.g., ¶ 0010). Further, the method of screening is for agents capable of modulating the activity of a CAP, including as said activity relates to cell proliferation. (e.g., ¶¶ 0011, 0191). The reference teaches that CAPs can be encoded by the nucleic acid sequences as depicted in Table 1, which discloses SEQ ID NO: 1223, whereby said sequence shares over 97% identity with instant SEQ ID NO: 1. Therefore, the reference teaches a nucleic acid sequence that encodes a polypeptide having amino acids that share about 60% identity with SEQ ID NO: 2. (See, attachment, Appendix A; depicting % identity matches for Result No. 1, ID NO: 1223, versus instant SEQ ID NO: 1).

Furthermore, the protein encoded by said DNA sequence can be a "recombinant protein". (e.g., ¶¶ 0026, 0080). Hereinafter, CAP should be construed as applying to the particular sequence, SEQ ID NO: 1223 (or instant SEQ ID NO:2) within the context of the base claims.

In addition, depending on the cancer, the reference teaches that DNA copy numbers can be increased/decreased. (e.g., ¶ 0206).

Therefore, measuring RNA expression levels will indirectly measure DNA synthesis (e.g., more copies of DNA correlating to higher expression levels, in the context of the anti-cancer effects of the test compound). In addition, the reference teaches a host of cancer cells that can be utilized in the screening methods, including lung cancer. (e.g., ¶¶ 0021-22).

More particularly, appropriate host cells include HeLa cells, which do not express p53 and is a transformed cell line (i.e., p53 null; claim 31). (e.g., ¶ 0077 bridging to p. 9). The candidate agent to be screened can be a nucleic acid molecule or an antisense molecule. (e.g., ¶ 0027, middle; ¶ 0201). Furthermore, candidate agents can be peptides as well as antibodies (e.g., ¶¶ 0194, 0209). Furthermore, agents are screened to determine whether they enhance or inhibit CAP activity. (e.g., ¶¶ 0193, 0195). The candidate agent can also be a substrate or ligand that binds CAP, whereby binding is measured in the screening assay. (e.g., ¶¶ 0189. 0200-202). In sum, Morris et al. anticipate the rejected claims.

Response to Arguments

Applicant's arguments have been fully considered but they are not persuasive. Essentially, Applicant arguments are as follows: (1) the sequence listing for Morris is not publicly available; (2) Morris does not ascribe MRE11 functionality or any to any of the 686 sequences disclosed; and (3) Morris does not recognize a MRE11 polypeptide thus not method of using MRE11 necessarily flows from the disclosure. (Remarks, pp. 10-11). In sum, Applicant's arguments appear to be based on whether Morris actually discloses MRE11.

With respect to Morris and the disclosed sequence for MRE11 – SEQ ID NO: 1224. It is noted that a copy of the sequence search report was inadvertently not attached to the Office Action mailed 04/19/2005. A copy of the report is attached herewith, disclosing the entire sequence for SEQ ID NO: 2 of the instant claims and SEQ ID NO: 1224 disclosed in Morris. The report demonstrates that said sequences are 100% identical. Thus, Morris necessarily discloses the MRE11 protein. As such the methods/steps disclosed also necessarily incorporate the disclosed protein (by virtue of the 100% identity to SEQ ID NO: 2).

Furthermore, regarding public availability, it is respectfully submitted that the sequence for instantly claimed SEQ ID NOs: 1 was publicly available as early as 1998, as displayed in the attached sequence search report for the GenEmbl database (Accession No. AF022778). In sum, the sequence disclosed in Morris is 100% identical to SEQ ID NO: 2 thus encodes MRE11 exclusively and was publically available well before the instant application's effective priority date of August 01, 2001.

Applicant's next two arguments hinge on whether MRE11 functionality is attributed to the disclosed sequences to which Morris refers in describing the assay methods disclosed. As alluded to in the preceding discussion, since Morris discloses a protein that is none other than the instantly claimed MRE11, then Morris's methods assaying an agent for affects on the disclosed protein necessarily assay effects of the compound on said MRE11 protein. As such, Morris anticipates the rejected claims.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ramin (Ray) Akhavan whose telephone number is 571-272-0766. The examiner can normally be reached on Monday-Friday from 8:30-5:30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully submitted,

Ray Akhavan/AU 1636